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*The Journal of Immunology*, 2001, 166: 270-276.




# Enhanced Secretion of IFN-γ by Activated Th1 Cells Occurs Via Reverse Signaling Through TNF-Related Activation-Induced Cytokine[1]

**Nien-Jung Chen[*], Mei-Wen Huang[*] and Shie-Liang Hsieh[2,*,†]**

[*] Department of Microbiology and Immunology, and [†] Immunology Research Center, National Yang-Ming University, Taipei, Taiwan

## Abstract



Growing evidence has demonstrated that members of TNF superfamily transduce signals after engagement with their receptors. TNF-related activation-induced cytokine (TRANCE), a member of TNF superfamily, is preferentially expressed on the surface of activated $CD4^+$ Th1 cells. The soluble receptor activator of NF-κB (RANK).Fc fusion protein suppresses IFN-γ secretion by activated Th1 cells, but does not affect IL-4 secretion by Th2 cells. The suppressive effect on IFN-γ secretion is observed when Th1 cells are activated by APCs, but not by immobilized anti-TCRß mAb. In contrast, immobilized RANK.Fc fusion protein augments IFN-γ secretion by Th1 cells, indicating the occurrence of reverse signaling through TRANCE during T cell/APC interaction. The enhanced secretion of IFN-γ mediated via TRANCE correlates with the activation of p38 mitogen-activated protein kinase and is blocked by SB203580, a p38 mitogen-activated protein kinase-specific inhibitor. Thus, in addition to its role in activating dendritic cells by binding to the receptor RANK, TRANCE itself can signal the augmentation of IFN-γ secretion via a p38-dependent pathway, and this provides yet another example of reverse signaling by a member of TNF superfamily.

## Introduction

# Expression of osteoclast differentiation signals by stromal elements of giant cell tumors.

**Atkins GJ, Haynes DR, Graves SE, Evdokiou A, Hay S, Bouralexis S, Findlay DM.**

Department of Orthopaedics and Trauma, University of Adelaide, South Australia.

The mechanisms by which primary tumors of the bone cause bone destruction have not been elucidated. Unlike most other lytic bone tumors, osteoclastomas, otherwise known as giant cell tumors (GCT), contain osteoclast-like cells within the tumor stroma. A new member of the TNF-ligand superfamily member, osteoclast differentiation factor (ODF/OPGL/RANKL/TRANCE), was recently identified. ODF was shown to directly stimulate osteoclastogenesis, in the presence of M-CSF. In this study, the expression of ODF was examined in a number of tumor samples associated with bone lysis in vivo. In addition, we investigated expression of the ODF receptor on osteoclast precursors, RANK, as well as the ODF inhibitor osteoprotegerin (OPG), and another TNF-ligand superfamily member, TRAIL, previously shown to abrogate the inhibitory effects of OPG. We report here the novel finding that GCT stromal cells contain abundant ODF mRNA, whereas the giant cell population exclusively expresses RANK mRNA. These results are consistent with the osteoclast-mediated bone destruction by these tumors. We also report the expression of OPG and TRAIL mRNA in GCT samples. A comparison with other lytic and nonlytic tumors of bone showed that GCT express more ODF and TRAIL mRNA relative to OPG mRNA. In addition, GCT were found to express a number of cytokines previously reported to play central roles in osteoclastogenesis, namely, IL-1, -6, -11, -17, as well as TNF-alpha. Importantly, GCT were also found to express high levels of M-CSF mRNA, a cytokine shown to be an essential cofactor of ODF, and a survival factor for mature and developing osteoclasts. Furthermore, expression of these molecules by stromal cells isolated from GCT continued in vitro. Thus GCT constitutively express all of the signals that are currently understood to be necessary for the differentiation of osteoclasts from precursor cells.

PMID: 10780856 [PubMed - indexed for MEDLINE]

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# Simultaneous block of interleukin-1 and tumor necrosis factor is required to completely prevent bone loss in the early postovariectomy period.

**Kimble RB, Matayoshi AB, Vannice JL, Kung VT, Williams C, Pacifici R.**

Division of Bone and Mineral Diseases, Washington University School of Medicine, St. Louis, Missouri, USA.

Considerable evidence supports the hypothesis that estrogen prevents bone loss by blocking the production of cytokines in bone or bone marrow. However, controversy remains on the role of candidate factors, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF). As IL-1 and TNF have many additive and/or synergistic effects in bone, we tested the hypothesis that the simultaneous block of IL-1 and TNF is required to prevent the initial phase of rapid bone loss that follows ovariectomy (ovx). To this aim, rats were ovariectomized and treated for 2 weeks with either IL-1 receptor antagonist (IL-1ra), an inhibitor of IL-1, or TNF-binding protein (TNFbp), an inhibitor of TNF. Ovx increased bone marrow cell secretion of IL-1 and TNF and decreased the bone density of the distal femur, as measured by dual energy x-ray absorptiometry. Ovx-induced bone loss was decreased by both IL-1ra and TNFbp and completely prevented by simultaneous treatment with IL-1ra and TNFbp. Combined treatment with IL-1ra and TNFbp decreased urinary pyridinoline cross-links, a marker of bone resorption that reflects osteoclast number and osteoclast activity, whereas treatment with either inhibitor alone was less effective. Both IL-1ra and TNFbp decreased the number of osteoclasts on the endocortical surfaces and stimulated bone formation, but the two inhibitors had no additive effects on these indexes, suggesting that inhibition of osteoclastogenesis and stimulation of bone formation do not account for the additive bone-sparing effects of IL-1ra and TNFbp. These inhibitors had no effect in sham-operated rats, indicating that they specifically blocked estrogen-dependent events. In conclusion, these data indicate that in the early post-ovx period, IL-1 and TNF play a critical causal role in inducing bone loss and do so by stimulating bone resorption and inhibiting bone formation.

PMID: 7789332 [PubMed - indexed for MEDLINE]

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# Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis.

**Delima AJ, Oates T, Assuma R, Schwartz Z, Cochran D, Amar S, Graves DT.**

Department of Periodontology and Oral Biology, Boston University School of Dental Medicine, MA, USA.

BACKGROUND, AIMS: Periodontal disease is a significant cause of tooth loss among adults and is characterized by the alteration and permanent destruction of the deeper periodontal tissues. Although the presence of pathologic microbes is required to trigger this process, the amplification and progression of the diseased state is believed to rely heavily on the production of host mediators in response to bacteria or their metabolic products. The inflammatory response is effective in preventing large-scale colonization of the gingival tissues by bacteria that lie in close proximity to the tooth surface or within the gingival sulcus. It has been postulated that the host-response in some individuals may lead to an over-reaction to invading oral pathogens resulting in the destruction of periodontal tissues. METHODS: Several host-derived mediators are believed to contribute to this response. Two agents considered to be essential in periodontal destruction are interleukin-1 (IL-1) and tumor necrosis factor (TNF). We investigated the role of IL-1 and TNF in the loss of connective tissue attachment in a Macaca fascicularis primate model of experimental periodontitis. Silk ligatures impregnated with the periodontal pathogen, Porphyromonas gingivalis were wrapped around the posterior teeth and the activity of IL-1 and TNF were inhibited by soluble receptors to these proinflammatory cytokines via local injection into interdental papillae. RESULTS: Histomorphometric analysis indicates that IL-1 and TNF antagonists significantly reduced the loss of connective tissue attachment by approximately 51% and the loss of alveolar bone height by almost 91%, both of which were statistically significant. CONCLUSION: This investigation demonstrates that the loss of connective tissue attachment and progression of periodontal disease can be retarded by antagonists to specific host mediators such as IL-1 and TNF and may provide a potential treatment modality to combat the disease process.

*Journal Of Clinical Periodontology* **28** (3), 233-240


Synergy

# Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis

**A. J. Delima[1], T. Oates[2], R. Assuma[1], Z. Schwartz[2,3], D. Cochran[2], S. Amar[1] and D. T. Graves[1]**


## Abstract

### Background, aims:

Periodontal disease is a significant cause of tooth loss among adults and is characterized by the alteration and permanent destruction of the deeper periodontal tissues. Although the presence of pathologic microbes is required to trigger this process, the amplification and progression of the diseased state is believed to rely heavily on the production of host mediators in response to bacteria or their metabolic products. The inflammatory response is effective in preventing large-scale colonization of the gingival tissues by bacteria that lie in close proximity to the tooth surface or within the gingival sulcus. It has been postulated that the host-response in some individuals may lead to an over-reaction to invading oral pathogens resulting in the destruction of periodontal tissues.

### Methods:

Several host-derived mediators are believed to contribute to this response. Two agents considered to be essential in periodontal destruction are interleukin-1 (IL-1) and tumor necrosis factor (TNF). We investigated the role of IL-1 and TNF in the loss of connective tissue attachment in a *Macaca fascicularis* primate model of experimental periodontitis. Silk ligatures





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impregnated with the periodontal pathogen, *Porphyromonas gingivalis* were wrapped around the posterior teeth and the activity of IL-1 and TNF were inhibited by soluble receptors to these proinflammatory cytokines via local injection into interdental papillae.

**Results:**

Histomorphometric analysis indicates that IL-1 and TNF antagonists significantly reduced the loss of connective tissue attachment by approximately 51% and the loss of alveolar bone height by almost 91%, both of which were statistically significant.

**Conclusion:**

This investigation demonstrates that the loss of connective tissue attachment and progression of periodontal disease can be retarded by antagonists to specific host mediators such as IL-1 and TNF and may provide a potential treatment modality to combat the disease process.



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